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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,002	05/20/2005	Ugur Sahin	4883-0001	7473

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

NOTIFICATION DATE	DELIVERY MODE
10/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/537,002	SAHIN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99,100,102-104 and 107-115* is/are pending in the application.

4a) Of the above claim(s) *107-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99, 100, 102-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed July 14, 2009 in response to the Office Action of February 14, 2008 is acknowledged and has been entered. Previously pending claims 101 has been cancelled and claims 100 and 102 have been amended. Claims 99, 100 and 102-104 are currently being examined.

Oath/Declaration

2. The Declaration under 37 CFR 1.132 filed July 14, 2008 is insufficient to overcome the rejection of claims 99, 100 and 102-104 based upon a lack of enablement under 35 USC 112 as set forth in the last Office action because although the expression of Claudin 18A2.1 mRNA appears to predictably correlate with the expression of Claudin 18A2.1 protein, German Application No. 102 54 601.0 teaches, as previously set forth, that the expression of Claudin 18A2.1 mRNA pancreatic cancer and pancreas are equivalent and the esophagus express significant amount of Claudin 18A2.1 mRNA, see Table 3 of German Application No. 102 54 601.0. Thus, one skill in the art would not predictably expect that the amount of Claudin 18A2.1 protein would be elevated compared to normal controls in pancreatic and esophageal cancer given that the normal pancreas and esophagus tissues appear to express amounts of Claudin 18A2.1 mRNA similar to those in Table 3 of the instant specification. Thus one of skill in the art would not believe it more likely than not that one could predictably diagnose pancreatic or esophageal cancer wherein detection of the tumor-associated antigen in a biological sample isolated from a patient in an amount greater than an amount of the tumor-associated antigen in a normal biological sample indicates the presence of cancer.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 99, 100 and 102-104 remain rejected under 35 USC 112 as lacking enablement essentially for the reasons previously set forth on pages 3-7, section 6 of the Office Action of February 14, 2008.

In the Office Action of February 14, 2008, Examiner Argued

Applicants argue that the Examiner has admitted that, "the specification is enabling for diagnosing stomach cancers and lung cancers by detecting the expression of Claudin-18A2 protein..." *(See,* page 4 of the Office Action dated June 27, 2007). The applicants agree. Applicants argue that diagnosing pancreatic and/or esophageal cancer is also enabled by the instant specification because the methodology for diagnosing these cancers would be the same as the methodology used for diagnosing stomach and lung cancers. Table 3A of the application as filed (also, "Tabelle 3A" on p. 74 of the published PCT application WO 2004/047863) shows thatClaudin-18A2 is overexpressed in pancreatic and esophageal cancers, similar to stomach and lung cancers. Applicants argue that thus, diagnosing pancreatic and esophageal cancers is also enabled by the instant specification and claims as filed.

Applicant's arguments have been fully considered and have not been found persuasive because, although the same methods would be used for detecting the protein in different cancers, given the lack of a predictable correlation of mRNA and protein expression and the heterogeneity of cancer phenotypes, as previously set forth, it cannot be predicted that the expression of Claudin-18A2 mRNA express in pancreatic and esophageal cancers predictably correlates with Claudin-18A2 protein/SEQ ID NO: 16 expression in the absence of empirical evidence showing that Claudin-18A2 protein/SEQ ID NO: 16 is expressed in pancreatic and esophageal cancers.

Additionally, upon review and reconsideration, the claims are not enabled for a method of diagnosing stomach cancer by detecting Claudin-18A2 in a biological sample isolated from a patient in an amount greater than an amount of Claudin-18A2 in a normal biological sample

because, as set forth in the 3rd paragraph of page 19 of the Office Action of October 17, 2006, because there is no increase in Claudin-18A2 protein in stomach cancer, just a change in the glycosylation status of Claudin-18A2, and there appears to be a decrease in the Claudin-18A2 protein level in stomach cancer compared to normal stomach, see Figure 30 of this Application or parental application WO 2004/047863. Additionally, Sanda et al. (J. Pathology 2006, 208:633-642) teach that in examining gastric cancer for Claudin-18 protein expression, that of the 20 gastric adenomas analyzed, 90% showed a decrease in Claudin 18 expression, see Abstract, p. 637, left col., Figure 4, Tables 3 and 4. The expression of Claudin 18 was detected with an antibody that recognizes the C-terminus of claudin 18 (see p. 634, right col., 2nd to last line), which would recognize both Claudin 18A1 and A2, which differ in the N-terminus, see p. 94, lines 19-20 of the instant specification and Figure 2 of Sanda et al.. However, Sanda et al. did not detect any claudin 18A1 mRNA in any of their gastric cancer samples using RT-PCR, see figure 3B, variant 1. Thus, the detected Claudin18 protein levels in gastric cancer are predictably those of Claudin 18A2. Given that neither the art nor the instant specification detect Claudin 18A2 in a greater amount in a stomach cancer versus normal tissue, and rather Claudin 18A2 is detected in lesser amounts compared to normal stomach tissue, one of skill in the art could not predictably use the claimed method for diagnosing stomach cancer without undue experimentation.

Applicants argue that the Examiner is of the opinion that Table 3 of the instant specification is drawn only to mRNA expression in the pancreas and esophageal cancer and that there is no predictable correlation between mRNA levels and protein levels (Advisory Action, page 2, paragraph 2). Applicants respectfully disagree with the Examiner's contention. Applicants respectfully direct the Examiner's attention to the instant specification which shows that increased mRNA expression of lung cancer *(See,* Table 3 and Figures 29-31) also correlates with increased Claudin-18A2 protein expression *(See,* page 98, lines25 - 29, and Figures 29-31 of the specification as filed). Applicants argue that of ordinary skill in the art would understand that the correlation between the increase in Claudin-18A2 mRNA expression with the increase in Claudin-18A2 protein expression would be expected in all cancer types that overexpress Claudin-18A2 mRNA *(i.e.,* the correlation would not be unique to lung cancer alone). Applicants argue that diagnosing pancreatic and esophageal cancers is also enabled by the instant

specification and claims as filed because there is a correlation between increased mRNA expression and increased protein expression of Claudin-18A2 in pancreatic and esophageal cancers.

Applicant's arguments have been fully considered and have not been found persuasive because of the lack of a predictable correlation of mRNA and protein expression and the heterogeneity of cancer phenotypes, as previously set forth, it cannot be predicted that the expression of Claudin-18A2 mRNA express in pancreatic and esophageal cancers predictably correlates with protein expression based only the expression of Claudin-18A2 mRNA and protein in lung cancer of in the absence of empirical evidence showing that Claudin-18A2 protein/SEQ ID NO: 16 is expressed in pancreatic and esophageal cancers. Additionally, Table 3 of the foreign priority docoment, German Application No. 102 54 601.0, page 58 of the original document and page 68 of the translated document, shows the level of expression of claudin 18A2.1 mRNA to be the same in pancreatic cancers and normal pancreatic tissue. Thus, it is unclear based on the teachings of the specification and priority documents if there are even changes in claudin 18A2.1 at the mRNA level in pancreatic cancer. Thus, even if it were found that mRNA levels correlated with protein levels, one of skill in the art would not predictably expect to diagnose pancreatic cancer based on the level of SEQ ID NO: 16 (claudin 18A2.1) given that it is unclear whether or not even if the mRNA encoding SEQ ID NO: 16 is increased in pancreatic cancer.

In the Remarks of July 14, 2008, Applicants argue:

Applicants argue that diagnosing pancreatic and/or esophageal cancer by the method of claim 99 is enabled by the instant specification. The subject application as filed clearly identifies Claudin-18A2 mRNA as being expressed in association with tumors, e.g., pancreas carcinoma and esophageal carcinoma, and not expressed in normal tissue, e.g., pancreas or esophagus tissue (see: Table 3a of the patent application as filed). For example, the presence of Claudin-18A2 mRNA has been correlated with the presence of Claudin-18A2 protein (SEQ ID NO: 16) in lung

carcinoma tissue (see: FIG. 24). Thus, the originally filed speciation enables a method according to claim 99 in the case of Claudin-18A2 since the presence of the mRNA is indicative of the presence of the corresponding protein.

Applicants argue that the Examiner alleges that protein expression cannot be predicted based on RNA expression data and cites for support of this statement Greenbaum et al. (2003, Genome Biology 4:117.1-117.8), Brennan et al. (1989, J. Autoimmunity 2 (suppl.): 177- 186), Zimmer (1991, Cell Motility and the Cytoskeleton 20:325-337), Hell et al. (1995, Laboratory Investigation 73:492-496), Fu et al. (1996, EMBO J. 15:4392-4401), Vallejo et al. (2000, Biochimie 82:1129-1133), and Jang et al. (1997, Clinical Exp. Metastasis 15:469-483); see pages 12 to 14 of the Office Action dated October 17, 2006; page 4, 2nd paragraph of the Office Action dated June 6, 2007; page 4, 2nd paragraph of the Office Action dated February 14, 2008. Applicants argue that in contrast to the Examiner's allegations, analysis of the cited documents shows that the majority of the cited references actually support that the presence or absence of mRNA is indicative of the presence or absence of protein, respectively (see: the Sahin Declaration, pages 3-5). Applicants submit herewith the Declaration of Professor Ugur Sahin, M.D. ("the Sahin Declaration") to address each of the Examiner's citations.

Applicants argue that Greenbaum et al. found in all instances that there is a positive mRNA- protein abundance correlation for ORFs studied. While Greenbaum et al. studied a quantitative correlation of mRNA with protein amounts, the instant patent application teaches a positive correlation between the presence of mRNA with the presence of the corresponding protein, that is, the presence of mRNA indicates the presence of protein, while the absence of mRNA indicates the absence of protein. Thus, in the instant application, it is only the absence or

presence of mRNA that should be indicative of the absence or presence of protein without regard to any quantitative correlation (see: the Sahin Declaration, page 3, point 5.1).

Applicants argue that Brennan et al. report an example where mRNA levels are high, and the respective proteins were not detected. However, Brennan et al. note with respect to this phenomenon that "more sensitive assays are clearly needed to explore this further"; see: page 182. Furthermore, since this publication is almost 20 years old, it appears that the apparent absence of protein is rather due to the insensitivity of the assay than due to an actual absence of protein (see: the Sahin Declaration, page 4, point 5.2).

Applicants argue that Zimmer observes that while the distribution of certain mRNAs paralleled the protein distribution in all muscles, there was no direct correlation between the mRNA and protein levels in different muscle types; see abstract. Thus, Zimmer clearly observes that the presence of mRNA is indicative for the presence of protein, i.e., qualitatively (see: the Sahin Declaration, page 4, point 5.3).

Applicants argue that Hell et al. describe a study on the expression of a specific gene relevant to Hodgkin's disease both at the protein and mRNA level. According to the results of the study, it appears that, while protein levels may vary, the presence of mRNA is indicative for the presence of protein in the study (see: the Sahin Declaration, page 4, point 5.4).

Applicants argue that Fu et al. report on a study on translational regulation of gene expression and find that while mRNA was present in all samples examined, the expression of the corresponding protein was variable from patient to patient. However, the studied transcription factor belongs to the category of regulatory proteins. Applicants submit herewith a reference by Guo et al. (2008, Acta Biochim Biophys Sin 40:426-436), which shows that genes belonging to

this category of regulation had non-significant and lowest mRNA protein expression correlations (see: e.g., abstract of Guo et al.). With respect to the claimed method, Claudin-18A2 is not a regulatory but rather is a structural protein. Thus, the phenomenon observed for by Fu et al. cannot be applied to Claudin-18A2, in particular, especially since it has been shown in the above patent application that presence of Claudin-18A2 mRNA indicates the presence of Claudin-18A2 protein, e.g. lung cancer (see: the Sahin Declaration, pages 4 and 5, point 5.5 and FIG 24 of the application as filed).

Applicants argue that Vallejo et al. have analyzed the expression of NRF-2 both at the mRNA and at the protein level and have found no correlation between NRF-2 mRNA and protein levels; see abstract. However, they clearly show that all samples do express NRF-2 protein. Thus, the presence of mRNA is indicative for the presence protein; see: Figure 1 and Table I. Furthermore, Vallejo et al. also show that there is perfect correlation between the mRNA and protein levels for Tfam and 13-actin; (see: Vallejo Figure 2 and Table I) (see: the Sahin Declaration, page 5, point 5.6).

Applicants argue that it appears that Jang et al. have not studied the correlation of mRNA and protein levels, since they state that further studies are required to establish whether changes in protein levels track with changes in mRNA levels for the investigated genes; see: abstract. Thus, Jang et al. cannot serve to substantiate the Examiner's argument. (see: the Sahin Declaration, page 5, point 5.7).

Applicants argue that The Sahin declaration describes that there is a consensus opinion in the field that even though the amount of mRNA may not reflect the amount of protein present in a cell, presence of mRNA is generally also indicative for presence of protein (see: the Sahin

Declaration, page 5, point 6 through point 6.4). Applicants argue that in the Sahin Declaration, Dr. Sahin provides support that it was, and still currently is, known in the field that the presence of mRNA is indicative for the presence of protein. (see: Tian et al. (2004, Molecular & Cellular Proteomics 3:960-969); Shankavaram et al. (2007, Mol. Cancer Ther. 6:820-832); Orntoft et al. (2002, Molecular & Cellular Proteomics 1:37-45); and Guo et al. (2008, Acta Biochim. Biophys. Sin. 40:426-436); attached herewith

Applicants argue that furthermore, genes of structural proteins, such as Claudin-18A2, are regulated by transcription rather than by translation. Thus, higher mRNA-protein correlation coefficients are generally observed for such proteins (see: the Sahin Declaration, page 7, Summary).

Applicants argue that in view of the fact that (i) Claudin-18A2 mRNA is not present at all in normal tissues except testis and stomach but is present in considerable amounts in several cancer types, (ii) there is no indication for a missing correlation between Claudin-18A2 mRNA and protein expression and (iii) a positive correlation between Claudin-18A2 mRNA and protein expression for normal lung tissue and lung cancer tissue, respectively, has been demonstrated in the above patent application, it is evident that Claudin-18A2 protein is a useful marker in the diagnosis of cancer for which presence of Claudin-18A2 mRNA is characteristic (see: the Sahin Declaration, page 7, Summary).

Applicants argue that one skilled in the art reading the instant specification in conjunction with common knowledge in the art would understand that the presence of Claudin-18A2 mRNA would be indicative of the presence of Claudin- 18A2 protein of SEQ ID NO: 16.

Applicants' arguments have been considered, but have not been found persuasive. Although the expression of Claudin 18A2.1 mRNA appears to predictably correlate with the expression of Claudin 18A2.1 protein, German Application No. 102 54 601.0 teaches, as previously set forth, that the expression of Claudin 18A2.1 mRNA pancreatic cancer and pancreas are equivalent and the esophagus express significant amount of Claudin 18A2.1 mRNA, see Table 3 of German Application No. 102 54 601.0. Thus, one skill in the art would not predictably expect that the amount of Claudin 18A2.1 protein would be elevated compared to normal controls in pancreatic and esophageal cancer given that the normal pancreas and esophagus tissues appear to express amounts of Claudin 18A2.1 mRNA similar to those in Table 3 of the instant specification. Thus one of skill in the art would not believe it more likely than not that one could predictably diagnose pancreatic or esophageal cancer wherein detection of the tumor-associated antigen in a biological sample isolated from a patient in an amount greater than an amount of the tumor-associated antigen in a normal biological sample indicates the presence of cancer.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Specification

4. It is noted that the Sequence Listing submitted July 14, 2008 was not accepted because of errors, see the notice sent August 14, 2008. Correction is required.

5. All other objections and rejections recited in the Office Action of February 14, 2008 are withdrawn.

6. No claims allowed.

7. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to

the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

/Karen A Canella/
Primary Examiner, Art Unit 1643

/PJR/